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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF
CARROLL ET AL.

Art Unit: 1647
Examiner: SEHARASEYON, JEGATHEESAN

APPLICATION NO: 09/813,329

FILED: MARCH 20, 2001

FOR: NOVEL DROSOPHILA TUMOR NECROSIS FACTOR CLASS MOLECULE ("DMTNFv2") POLYNUCLEOTIDES AND VARIANTS THEREOF

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION PURSUANT TO 37 C.F.R. §1.132

Sir:

1. I, Pamela M. Carroll, Ph.D., am an applicant of the patent application Serial No. 09/813,329 identified above and co-inventor of the subject matter described and claimed in this patent application.

2. A true and accurate copy of my *curriculum vitae*, which evidences my expertise and credentials, is attached herewith and labeled **Exhibit A**.

3. I have performed an experiment, or directed or caused an experiment to be performed, to provide additional evidence that the claimed DmTNFv2 polynucleotides encode a polypeptide that represents a potent inducer of apoptosis. We and others have found that targeted overexpression of DmTNFv2 causes excessive cell death and ablation of tissue in the tissues in which DmTNFv2 is expressed.

Briefly, the pro-apoptotic activity of DmTNFv2 was demonstrated by comparing the eyes of transgenic flies that overexpress the DmTNFv2 polypeptide using a GAL4 eye-specific promoter, to transgenic flies containing the GAL4 construct alone. The GAL4 construct that was used for these

experiments harbors a GMR promoter that overexpresses GAL4 in the eye imaginal disc (premordial eye) in 1st instar larvae. Flies containing the (GMR-Gal4) genotype were crossed to transgenic flies expressing UAS sites adjacent to the DmTNFv2 cDNA. Activation of the GMR promoter controls the expression of GAL4 transcriptional activators, and results in increased Gal4 protein production. The Gal4 protein binds to the UAS sites and results in the subsequent increase of DmTNFv2 transcription.

The results of this experiment are presented in **Exhibit B**. **Exhibit B,** slide "a", shows adult Drosophila eyes that express only GMR-GAL4. As shown, (GMR-GAL4) genotype flies have a wild-type phenotype. **Exhibit B**, slide "b", shows adult flies containing the (GMR-GAL4; UAS-DmTNFv2) genotype. The phenotype of (GMR-GAL4; UAS- DmTNFv2) flies is massive cell death of the eye. This result is consistent with DmTNFv2 representing a TNF molecule and supportive of the asserted utilities in the instant specification.

4. The following comments relate to **Exhibit B**. DmTNFv2 is the only TNF molecule that has been identified in the completed Drosophila genome by us as well as others. The fact that only one TNF molecule had been identified strongly suggested to us that TNF signaling would be conserved in the ancestral DmTNFv2 protein function. DmTNFv2 has the structural similarities associated with TNF molecules including a distinct C-terminal TNF domain and a hydrophobic transmembrane domain, the main features of all TNF molecules. The C-terminal TNF domain of DmTNFv2 shows homology to other TNF family members at a level of identity comparable to the homology observed amongst mammalian TNF family members themselves (approximately 20-25% identity) (Locksley et al., Cell *104*, 487-501 (2001); Moreno et al., Curr Biol *12*, 1263-1268 (2002); submitted concurrently herewith). The pro-apoptotic activity of the DmTNFv2 polypeptide demonstrated in **Exhibit B** is directly analogous to the pro-apoptotic activity of mammalian orthologs of Tumor Necrosis Factor (TNF) molecules. In mammals, at least 6 TNF-like molecules are known to be able to stimulate apoptosis through activation of established apoptotic pathways (Locksley et al, *Cell* **104**, 487-501. (2001); submitted concurrently herewith). This experiment demonstrates, unequivocally, that, DmTNFv2, is a pro—apoptotic molecule that elicits a phenotype consistent with a TNF –family member upon overexpression. Importantly, post-filing publications of the DmTNFv2 polypeptide (referred to as "eiger" in Igaki et al., Embo J *21*, 3009-3018 (2002); and Moreno et al., Curr Biol *12*, 1263-1268 (2002); submitted concurrently herewith) show that the massive cell death eye phenotype has many hallmarks of apoptosis, including staining for acridine orange, a commonly used marker for apoptotic cell death, in addition to demonstrating that this eye phenotype can be blocked by inhibitors of apoptosis proteins (IAPs). (Igaki et al., 2002; Moreno et al., 2002; submitted concurrently herewith). The overexpression system used in our experiments is

exactly the same as the system used and described by Igaki et al and Moreno et al and supports the asserted utilities and results described in the instant specification as well as the results submitted herewith.

5. Drosophila orthologs of the mammalian TNF signaling pathway are known to exist and are illustrated in **Exhibit C**.

6. The following comments relate to **Exhibit C**. TNF activation of a TNF receptor system has been known to trigger several distinct intracellular pathways in mammals including Rel/NF-KappaB (NF-KB) (referred to hereafter as Rel), c-Jun N-terminal kinase (JNK) and p38 protein kinase cascade (reviewed in Varfolomeev and Ashkenazi, Cell *116*, 491-497 (2004); submitted concurrently herewith) . Established members of these pathways have been found in Drosophila, demonstrating that the signaling pathways are, in fact, maintained in this organism. JNK signaling is required for a variety of biological processes in flies and mammals, including apoptosis and immunity (see Stronach and Perrimon Oncogene 18:6172-6182 (1999), and Chang and Karin, Nature 410:37-40 (2001); submitted concurrently herewith); submitted concurrently herewith). Ectopic JNK activation in Drosophila causes excessive cell death and tissue ablation which is similar to the results observed in **Exhibit B** for overexpressed DmTNFv2 (reviewed in Varfolomeev and Ashkenazi, Cell *116*, 491-497 (2004); submitted concurrently herewith)

7. I have performed an experiment, or directed or caused an experiment to be performed, to provide additional evidence that the claimed DmTNFv2 polynucleotides encode a polypeptide that functions in the JNK pathway. We and others have found that the excessive cell death and tissue ablation phenotype observed in transgenic flies that overexpress DmTNFv2 is a.) suppressed in fly genotypes containing a mutation in JNK kinase, and b.) is enhanced in fly genotypes containing a mutation in Puc. This experiment was performed using methods similar to the methods described in Moreno et al.

Briefly, DmTNFv2 cDNA was cloned into a UAS transgene based on the pUAS construct (Brand and Perrimon, Development *118*, 401-415 (1993); submitted concurrently herewith). A Gal4 construct containing the GMR eye-specific promoter, as described above for the **Exhibit B** experiments, was utilized (Hay et al., Proc Natl Acad Sci U S A *94*, 5195-5200 (1997); submitted concurrently herewith). The UAS- DmTNFv2 transgene was used to transfect wild-type flies, and mutant flies containing a deletion of JNK kinase, in addition to mutant flies containing a deletion of

Puc were obtained from Exelixis Inc. and recently published in Parks et al (Nature Genetics, 36:288-292 (2004); submitted concurrently herewith).

The results of this experiment are presented in **Exhibit D**. **Exhibit D**, slide "a", shows an adult fly eye containing the (GMR-GAL4; UAS- DmTNFv2) genotype (Brand and Perrimon, Development *118*, 401-415 (1993); submitted concurrently herewith). As demonstrated in **Exhibit B**, (GMR-GAL4; UAS- DmTNFv2) genotype flies result in a massive cell death eye phenotype. However, slide "b" of Exhibit D demonstrates that the massive cell death eye phenotype is suppressed in flies containing a mutation in JNK kinase. In Exhibit D, slide "c", flies containing a mutation in Puc, a negative regulator of JNK kinases, is demonstrated to enhance the massive cell death eye phenotype observed in slide "a". The genotype of the flies illustrated in Exhibit D, slide "a", slide "b", and slide "c", is (GMR-GAL4; UAS- DmTNFv2); (GMR-GAL4; UAS- DmTNFv2; deletion of JNK region); and (GMR-GAL4; UAS- DmTNFv2; deletion of Puc region); respectively.

8. The following comments relate to **Exhibit D**. The central and widely accepted concept in these genetic interactions is that, if a mutation in one gene (in this case JNK or puc deletions) suppresses or enhances the phenotype of another gene (in this case DmTNFv2), their products are believed to be directly involved in the same process. (Carroll et al., Pharmacol Ther *99*, 183-220 (2003); submitted concurrently herewith). Based upon this paradigm and in consideration of the results observed in **Exhibit D**, JNK and puc are believed to be in the same pathway as DmTNFv2. Moreover, the DmTNFv2 and JNK observations are directly analogous to the respective roles of TNF and JNK in mammalian system TNF pathways. Two post-filing publications have found that DmTNFv2 stimulates apoptosis through a JNK-dependent mechanism and is consistent with our findings. (Igaki et al., 2002; Moreno et al., 2002); submitted concurrently herewith). A similar inhibitory role of JNK has been demonstrated in mammalian TNF-induced cell death. (Wajant and Scheurich, Prog Mol Subcell Biol *34*, 47-72 (2004); submitted concurrently herewith).

9. I have performed an experiment, or directed or caused an experiment to be performed, to provide additional evidence that the claimed DmTNFv2 polynucleotides are tightly controlled by Toll and Dorsal activation within the Rel pathway with important implications to innate immunity in both flies and humans. The methods and results of this experiment are described in the instant specification, U.S. Serial No. 09/813,329 (see Figure 9), and are discussed herein to provide additional context in consideration of the other Exhibits provided herewith.

Briefly, Drosophila embryos were hybridized with digoxigenin-labeled antisense probes specific for DmTNFv2 and stained to visualize gene expression using whole mount In situ

hybridization assays. Wild type embryos, in addition to two mutant embryos harboring either a Toll mutation (Tl3) or a Dorsal null mutation (dl1) were utilized. The Toll mutation in Tl3 embryos (genotype: Tl3/+) causes constitutive activation of Toll and nuclear transport of Dorsal throughout the embryo, while the dl1 mutants (genotype: dl1/dl1) are null mutants that result in loss-of-function of the Dorsal gene. Flies containing dominant TL3 and Dorsal loss-of-function mutations were obtained from the FlyBase public stock center at Bloomington, Indiana.

The results of this experiment are presented in **Exhibit E**. **Exhibit E**, slide "a", shows that DmTNFv2 is localized to the ventral side of wild-type embryos. **Exhibit E**, slide "b", shows that the ventral DmTNFv2 expression is lost in Toll mutant (Tl3 mutant) embryos. The posterior tip expression has been noted by others with genes that are expressed in the ventral-side of the embryo and misregulated by Dorsal (Belvin and Anderson, Annu Rev Cell Dev Biol *12*, 393-416 (1996); submitted concurrently herewith). Exhibit E, slide "c" shows DmTNFv2 expression in Dorsal null mutants (dl1 mutant). As shown, in the absence of the functional Dorsal protein, DmTNFv2 is shown to be expressed throughout the embryo and completely loses the ventral-specific expression seen in slide "a" of **Exhibit E**.

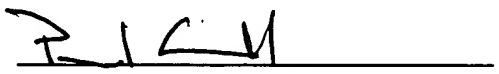
10. The following comments relate to **Exhibit E**. The Drosophila Toll protein is a transmembrane protein, originally characterized to establish dorsal-ventral polarity during development, that mediates resistance to the invasion of pathogenic microorganisms in Drosophila by activating the Rel pathways, Dorsal and Dif. Activation of these Rel pathways induces expression of a distinct set of genes that encode antimicrobial peptides. Recently, mammalian homologues of Toll, designated as Toll-like receptors (TLRs) have been discovered to be essential for the recognition of pathogens that trigger the mammalian innate response. Recognition of pathogens by TLRs elicits the activation of an intracellular signaling cascade leading to activation of JNK and Rel pathways (Takeuchi and Akira, Int Immunopharmacol *1*, 625-635 (2001); submitted concurrently herewith). In mammals, JNK activation is required for innate immunity and inflammation-induced apoptosis, however, this response is negatively regulated by Rel signaling. The cross-talk between JNK and rel pathways in mammals is thought to be critical in maintaining an immune system that does not over respond to stimulus. (Kyriakis, Nature *414*, 265-266 (2001); submitted concurrently herewith). In Drosophila, the bacterial mimic lipoploysaccride (LPS) has been reported to activate JNK and Rel pathways which is required for a subset of Drosophila immune response genes (Boutros et al., Dev Cell *3*, 711-722 (2002); submitted concurrently herewith). Further supporting evidence that the Drosophila TNF pathway and function is analogous to mammalian TNF pathways and function has been demonstrated by Park et al. where activation

of Rel in Drosophila was found to lead to attenuation of JNK activity after LPS challenge (Park et al., Genes Dev *18*, 584-594 (2004); submitted concurrently herewith).

The results showing tight regulation of DmTNFv2 gene expression in dorsal-ventral polarity in Drosophila imply a role in innate immunity (as shown in Exhibit E and disclosed in U.S. Serial No. 09/813,329). Toll's activation of the Rel pathway is similar in both innate immunity and dorsal-ventral polarity functions (Takeuchi and Akira, Int Immunopharmacol *1*, 625-635 (2001); submitted concurrently herewith), thus, dorsal-ventral polarity regulation with maternally deposited proteins serves as a surrogate system for innate immunity. In early Drosophila development, Dorsal, a member of the Rel family of transcription factors, is distributed throughout the cytoplasm in oocytes. In post-fertilized embryos, activation of Toll leads to Dorsal transport to the nucleus. (Belvin, Annu Rev Cell Dev Biol *12*, 393-416 (1996); submitted concurrently herewith). This Toll-regulated nuclear transport of Dorsal leads to the formation of a Dorsal activity gradient with peak activity in the ventral region and lowest activity in the dorsal region. **Exhibit E** shows that DmTNFv2 is only expressed when there is very low Dorsal activity. In mutants where Dorsal is nuclear (Tl3 mutants), ventrally localized DmTNFv2 mRNA is not found . The data shown in **Exhibit E** has recently been corroborated by another group (see Stathopoulos, Cell, 111(5):687-701 (2002); submitted concurrently herewith). The tight regulation of DmTNFv2 by NF-KB/rel activation indicates that DmTNFv2 is an important mediator of Drosophila innate immunity. These results are directly analogous to mammalian TNFs expressed in the immune system, where their rapid and potent signaling capabilities are tightly controlled.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Respectfully submitted,



Pamela M. Carroll, Ph.D.

5/27/04

Date

Enclosures: Exhibits A, B, C, D, and E.

Exhibit A

Pamela Carroll, Ph.D.

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PROFESSIONAL EXPERIENCE

10/98-1/01	Bristol-Myers Squibb, Princeton, New Jersey Applied Genomics Research Investigator
1/01-6/03	Senior Research Investigator I
6/03-present	Senior Research Investigator II

Applied Genomics Responsibilities:

- Lead a group of scientists in the discovery and validation of new drug targets, and mechanism of action studies. Technology platforms include high-content screening for multi-parameter measurements in cellular systems (Cellomics), medium-throughput cell biological assays, RNAi-based genetic screening, RNA profiling (Affymetrix), and genetic model systems.
- Strong expertise and knowledge base in cell signaling and apoptosis. Current focus of laboratory are EGF, TNF, NF-κB, β-catenin, PTEN, and p53 pathways.
- Lead liaison for all Applied Genomics projects with oncology and immunology departments. Responsible for interfacing with biology and toxicology groups to provide expertise and enable the full utilization of genomic resources.
- Supervise Research Scientists, and thesis advisor for a Princeton University Doctoral student. Doctoral student thesis project involves systems biology approaches to modeling Epidermal Growth Factor signaling.
- Initiated and continue to lead a Drosophila research group to leverage models organisms in drug discovery.
- Developed high-throughput Drosophila genetic screens for discovery of novel components in disease-relevant pathways.
- Developed cell-based genetic screens with RNA interference technologies. Successful screens included discovery of new essential immunomodulating molecules that are being developed as target for inflammatory diseases. Initiated first RNAi studies at BMS.
- Developed a gene disruption system in Drosophila using zinc-finger proteins designed to control a gene's expression.
- Design and analysis of transcriptional profiling experiments.

External Alliance Management:

- Alliance manager for 5-year Exelixis Mechanism of Action Alliance (1999-2004) and Sangamo Technology Alliance (2000-2002). Involved in all aspects of alliance including negotiation of alliance terms, managing projects, and communicating results within Bristol-Myers Squibb. Alliance discovered mechanism of action of several compounds and delivered novel targets that transitioned into the early discovery pipeline.
- Member of the Leadership Team for the BMS-Exelixis Oncology collaboration (2001-2008). Role includes implementing cell biological target validation strategies and contributing expertise in model systems. Initially involved in negotiations of terms of contract.
- Member of the Target Validation Committee that formulates a global target validation strategy by assessing technology opportunities valuable to fast track research on novel gene functions. Led to eight alliance collaborations.
- Continue to support evaluation of external licensing opportunities and external technologies.
- Initiated and manage academic collaborations with Harvard Medical School, Rutgers University, Princeton University and the University of Florida.
- Implemented and currently managing an outsourced project in cardiovascular drug safety and teratogenicity with zebrafish model systems.

1/94-10/98 Stanford University, Stanford, California
Department of Biological Sciences
Postdoctoral Fellow
Advisor: Dr. Michael Simon

- Identified a novel tyrosine-phosphatase signal transduction pathway downstream of Drosophila receptor tyrosine kinases.
- Conducted large-scale genetic screen to identify the novel pathway and cloned mutant loci.
- Genetic and biochemical strategies were used to dissect phosphatase pathway.

9/88-12/93 State University of New York at Stony Brook
Department of Cellular and Developmental Biology
Graduate Student
Advisor: Dr. Sidney Strickland

- Studied the biological role of the serine protease tissue plasminogen activator (tPA) during mouse development.
- Discovered and characterized a tPA cell surface receptor.
- Used transgenic mice to study tPA function and transcriptional regulation in embryogenesis and in the adult central nervous system.

1/86-9/87 National Cancer Institute, Bethesda, Maryland
Laboratory of Cellular Carcinogenesis and Tumor Promotion
Research Technician

- Investigated protein kinase C (PKC) function in NADPH-oxidase activation in isolated human neutrophils.

EDUCATION

1993 State University of New York at Stony Brook
Program in Cellular and Developmental Biology
Degree awarded: Ph.D.
Advisor: Dr. Sidney Strickland
Thesis Title: "The role of tissue plasminogen activator in mouse development"

1985 Saint Michael's College, Winooski Park, Vermont
Degree awarded: Bachelor of Arts
Major: Biology

PUBLIC RELATIONS EXPERIENCE

- Trained by Franchetti Communications for interactions with local, national and international news organizations. One of two scientists selected to represent BMS in the media.
- Featured in nationally televised commercial for Pharmaceutical Research and Manufacturers of America (PhRMA) in Spring 2002.
- Interviewed with journalists leading to several feature articles including Business Week, Nature Drug Discovery, Time Magazine, Forbes, Wall Street Journal, Continental Air Magazine, In Vivo, and Sky TV.
- Selected to interact on behalf of BMS in community affairs and local schools.
- Research featured in recruitment and community affairs campaign.

OTHER PROFESSIONAL EXPERIENCE

- External Advisory Board, University of Arizona Professional Graduate Program in Sciences. Appointed in 2000.
- Board of Directors, Hartnett Science Fund, Saint Michael's College. Appointed in 2002.

- **Invited speaker** (since 1998)
  - Drug Discovery World Congress, August 2004
  - Princeton University, Lecturer, Biological Networks (Graduate level) 2003, 2004
  - Preclinical Development Forum, IBC, March 2004
  - Princeton University, Department of Chemical Engineering, May 2003
  - Rider University, March 2003
  - Genomes on Target, Cambridge Healthtech Institute, November 2002
  - Imperial Research Cancer Foundation, September 2001
  - University of Pennsylvania, Department of Neurobiology, April 2001
  - University of Arizona, Cancer Research Institute, January 2001
  - International Drosophila Conference, April 2000
  - Princeton University, Department of Molecular Biology, April 1999
  - The College of New Jersey, March 1999

HONORS AND AWARDS

- Collaboration Award for implementing a target validation strategy for over 100 new targets in Cancer, July 2003.
- Triumph Award for identifying and managing external target validation alliances. Part of first recipient team of this Bristol-Myers Squibb award, August 2002.
- National Research Service Award, National Institutes of Health, 1994-1997.
- Sigma Xi Dissertation Award, 1993.
- Award of Academic Excellence, Saint Michael's College, 1985.

PATENTS

- "Novel Drosophila Tumor Necrosis Factor Class Molecule and Variants." US 20020012968.
- "Modulators of Rab GeranylGeranyl Transferase and methods of use thereof" WO2004015130
- "Polynucleotide encoding an activated human T-lymphocyte-derived protein related to ubiquitin conjugationg enzyme. US20030190613
- "Polynucleotide encoding a novel human potassium channel beta-subunit, K+ betaM2" US20030032786 and WO2002066601
- "Polynucleotide encoding a novel human potassium channel beta-subunit, K+ betaM3" US20030114371 and WO2002068587
- "Polynucleotide encoding a novel human potassium channel beta-subunit, K+ betaM4 and M5" US20030054989 and WO2002068604
- 3 provisional patents submitted.

PUBLICATIONS

Carroll, P. M.*, Chan,G.*, Yuan, R.*, Xiao, H., Guan, B., He, A., Kayne, P., Handler, A. M., and Zhou, L. Coordinated genomic responses mediate irradiation-induced apoptosis (Manuscript submitted).

Jamieson, A., Guan, B., Craddick, T. J., Xiao, H., Wolffe, A. and **Carroll, P. M.** Controlling gene expression in Drosophila using a Methyl-Binding Domain and engineered zinc-finger proteins. (Manuscript submitted).

Kindt R., **Carroll P. M.**, Moore L., Zhang Y., Ross-Macdonald P., Cockett, M. C., and Fitzgerald, K. Inhibition of RGS/Gq downstream of GPCR signals via a novel mechanism. (Manuscript in preparation).

Exhibit A

Carroll, P.M.*, Lackner, M. R.*, Kindt, R.*, Fitzgerald, K., Costa, M, Hung, T., Maxwell, M. E ., Manne, V., Costa, M., Guan, B., Reddy, R., Brown, K., Cockett, M. C. and Ross-Macdonald, P. Ras Farnesyl Transferase inhibitors modulate apoptosis through inhibiting Rab Geranyl-Geranyl Transferases (manuscript in preparation).

Carroll, P. M. and Fitzgerald, K. (editors) Model Organisms Research in Drug Discovery. Wiley and Son Publishers (London) 2003. ISBN 0470848936

Carroll, P. M., Fitzgerald, K., and Kindt, R. Chemical Genetics: Bridging the gap between genomics and drug Discovery with C.*elegans* and *Drosophila.* A Chapter in "Model Organisms in Drug Discovery". Wiley and Son Publishers (London) 2003.

Fitzgerald, K. and **Carroll, P. M.** Introduction to Model Organisms in Drug Discovery. A Chapter in "Model Organisms in Drug Discovery" Wiley and Son Publishers (London) 2003. ISBN 0470848936.

Carroll, P. M. *, Dougherty, B.*; Ross-Macdonald, P.*, Browman, K., and FitzGerald, K. Model systems in drug discovery: chemical genetics meets genomics. Pharmacol Ther. 2003 Aug; *99*(2):183-220.

Smith, R. K., **Carroll, P. M.**, Allard, J. D., and Simon, M. A. (2002). MASK, a large ankyrin repeat and KH domain-containing protein involved in Drosophila receptor tyrosine kinase signaling. Development *129*, 71-82.

Allard, J. D., Herbst, R., **Carroll, P. M.**, and Simon, M. A. (1998). Mutational analysis of the SRC homology 2 domain protein-tyrosine phosphatase Corkscrew. J Biol Chem *273*, 13129-13135.

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Carroll, P. M.*, Tsirka, S. E.*, Richards, W. G., Frohman, M. A., and Strickland, S. (1994). The mouse tissue plasminogen activator gene 5' flanking region directs appropriate expression in development and a seizure-enhanced response in the CNS. Development *120*, 3173-3183.

Carroll, P. M., Richards, W. G., Darrow, A. L., Wells, J. M., and Strickland, S. (1993). Preimplantation mouse embryos express a cell surface receptor for tissue-plasminogen activator. Development *119*, 191-198.

Richards, W. G., **Carroll, P. M.,** Kinloch, R. A., Wassarman, P. M., and Strickland, S. (1993). Creating maternal effect mutations in transgenic mice: antisense inhibition of an oocyte gene product. Dev Biol *160*, 543-553.

Anderson, S. M., **Carroll, P. M.**, and Lee, F. D. (1990). Abrogation of IL-3 dependent growth requires a functional v-src gene product: evidence for an autocrine growth cycle. Oncogene *5*, 317-325.

Tauber, A. I., Cox, J. A., Curnutte, J. T., **Carroll, P. M.**, Nakakuma, H., Warren, B., Gilbert, H., and Blumberg, P. M. (1989). Activation of human neutrophil NADPH-oxidase in vitro by the catalytic fragment of protein kinase-C. Biochem Biophys Res Commun *158*, 884-890.

* Authors contributed equally.

Exhibit C

TNF (DmTNFv2 and Eiger) → TNF Receptor (Wengen) → TRAF2 (DTRAF)→JNKK (HEP) → JNK (Bsk) → Jun and Fos (DJun and DFos) → JNK phosphatase (Puc